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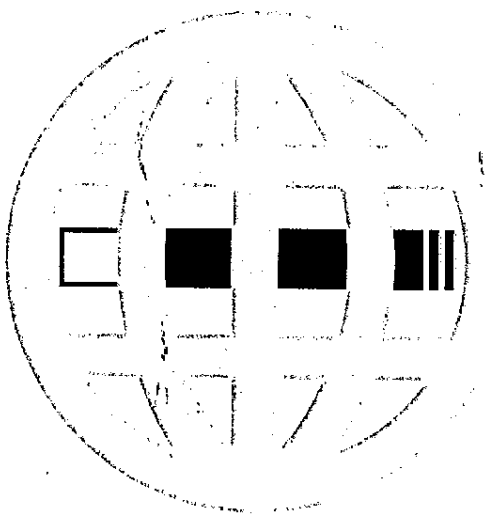
The Global War



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CAN WE PREDICT DISEASE IN THE FUTURE?

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The question that I have been asked to address may seem redundant at a meeting to which people have come from all over the world with the single object of reducing the risk of ill health due to smoking. For few would have troubled to come had they not thought that it was possible to predict that an increase in the consumption of tobacco would increase the incidence of several important diseases and that a reduction would reduce it. I shall, therefore, anticipate my conclusion and assert now that prediction along these lines is certainly possible. The question is not, however, altogether idle, as the relationships between smoking and the risk of disease are often complex and the incidence of some smoking related diseases may change in unexpected ways. I shall, therefore, seek to define the limits of our ability to predict the effects of changing smoking habits, leaving to Ernst Wynder and Richard Peto the quantitative estimate of the holocaust that smoking has produced in some countries and must be expected to produce in others, if tobacco salesmen achieve their targets.

DISEASES CAUSED BY SMOKING

Consider first the multiplicity of diseases that are caused by smoking, principally by the smoking of cigarettes, but many also, though usually to a smaller extent, by the smoking of pipes and cigars and by the variety of tobacco products intermediate between cigars and cigarettes that are characteristic of particular areas. By "caused by smoking" I do not, of course, mean to imply that smoking is either necessary or sufficient to produce these diseases. That would be obviously untrue. What I mean is what is ordinarily meant in preventive medicine: namely, that other things being equal the risk of each disease will be increased if individuals smoke more and reduced if they smoke less. For some diseases caused by smoking, the contribution of smoking to the total risk of developing the disease may be small; for others it may be great. For none, as far as I know, is smoking or other forms of tobacco use the only cause unless we allow that nicotine addiction is a disease.

The many diseases that are caused by smoking in this sense include the eight diseases listed in Table 1 that have been assessed as caused by smoking by the International Agency for Research on Cancer (1986) and six others that I have listed as possibly caused by smoking, for which there is accumulating evidence of a causal relationship, even though the increased incidence in heavy cigarette smokers may be less than double that in lifelong non-smokers, as in the case of myeloid leukemia and cancer of the stomach, or, if more than double, attributed in part to confounding with other aetiological agents, as in the case of cancer of the liver.

Table 1

CANCERS CAUSED BY SMOKING

Definitely caused (IARC 1986)

Cancers of mouth, pharynx, oesophagus, larynx, lung, bladder, renal pelvis, and pancreas

Possibly caused

Cancers of nasal sinuses, stomach, liver, body of kidney, and cervix uteri, and myeloid leukemia

The many vascular and respiratory diseases that are produced by smoking, which in many countries account for more smoking induced deaths than cancer, are listed in Table 2. The idea that all of them were actually caused by smoking or, in the case of pulmonary tuberculosis, exacerbated by smoking, took many years to establish; but no serious student of the subject now questions the role of smoking in relation to vascular disease as a whole any more than he does its obvious role in relation to disease of the bronchi and lung.

Table 2

VASCULAR AND RESPIRATORY DISEASES CAUSED OR AGGRAVATED BY SMOKING

Vascular

Ischaemic heart disease, pulmonary heart disease, "myocardial degeneration", aortic aneurysm, peripheral vascular disease, cerebral thrombosis and haemorrhage, subarachnoid haemorrhage, arteriosclerosis, and hypertensive stroke

Respiratory

Chronic obstructive lung disease (chronic bronchitis and emphysema), pneumonia, and pulmonary tuberculosis.

Lastly there are listed in Table 3, seven miscellaneous conditions that are caused or aggravated by smoking, to which others may well be added in the course of time. These, it will be noted, include hernia for which as yet the evidence is slight; but it is difficult not to believe that it is aggravated by a smoker's cough.

Table 3

OTHER CONDITIONS CAUSED OR AGGRAVATED BY SMOKING

Gastric and duodenal ulcers

Crohn's disease

Hernia

Osteoporosis

Accidental burning

Retarded fetal growth

TRENDS IN TOBACCO CONSUMPTION AND MORTALITY

For some of these diseases or conditions the role of smoking is relatively minor and we can hardly expect the trends in their incidence to reflect at all closely the trends in the consumption of tobacco, since they could be obscured by contrary trends in the prevalence of other and more important causes related to people's behaviour or the environment. For others, however, the incidence of which is several times higher in continuing cigarette smokers than in life-long non-smokers, the situation is different. For these, smoking is a major cause and the trends in their incidence might be expected to be roughly similar to, even if they did not exactly parallel, the trends in the consumption of tobacco. Seven such diseases are listed in Table 4. For each, the mortality in current cigarette smokers has been 4 or more times that in life-long non-smokers in a cohort of 34,000 British doctors that has now been followed for 35 years from 1951 to 1986 (Doll, Gray, Peto, and Wheatley, personal communication) and also (if reported separately) in the American Cancer Society's studies of a million Americans (Surgeon General, 1989).

Table 4

DISEASES CLOSELY RELATED TO SMOKING (MEN)

Disease	Relative risk: continuing cigarette smokers to life-long non-smokers	
	British male doctors 1951-86[1]	American men 1982-86[2]
Cancer of mouth & pharynx	14.5	27.5
* oesophagus	15.0	7.6
* larynx	∞	10.5
* lung	13.6	22.4
Chronic obstructive lung disease	11.1	9.7
Pulmonary tuberculosis	4.0	-
Aortic aneurysm	4.3	4.1

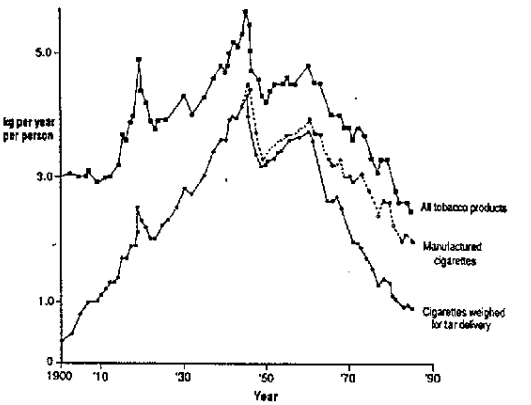
[1] Doll, Gray, Peto, and Wheatley, personal communication.
[2] American Cancer Society. See: Surgeon General (1989).

The trends in these diseases vary from one country to another and I have chosen to study the trends in the UK, partly because they reflect both the waxing and waning of the smoking epidemic and partly because the population is large enough for the numbers of deaths that occur each year from relatively uncommon diseases to be little affected by random fluctuation.

Tobacco consumption by men

The trends in the annual per caput consumption by men of tobacco products, manufactured cigarettes, and manufactured cigarettes weighted for tar delivery, are shown for an 85 year period in Fig. 1. From this it is seen that all these variables reached their maximum in 1945, that the consumption of all tobacco products never quite doubled the amount that it had already reached in 1900, that cigarette consumption increased enormously in the first half of the century and has decreased progressively since 1960, and that total tar delivery in cigarettes, if all types of cigarettes are smoked in a standard way, is now down to a little less than it was in 1910: that is, on the assumption that the mean tar delivery per cigarette was constant in the first three decades before any measurements were made.

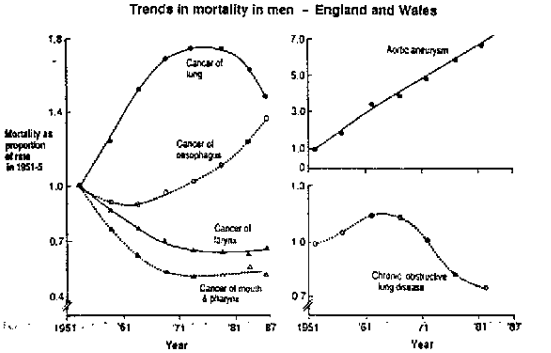
Trend in consumption of tobacco by men in U.K.



Mortality of men

Incidence rates that are sufficiently reliable are not unfortunately available over a long enough period for the purpose of examining long term trends and we have to rely on mortality rates with the added complication that they will be affected by changes in the efficacy of treatment as well as by changes in the incidence of the underlying disease. In fact there has been very little improvement in the efficacy of treatment for any of the categories of disease that were listed in Table 4, apart from pulmonary tuberculosis, and improvements in treatment can have had little effect on the trend in mortality for the remaining six. The trends for these diseases over 37 years from 1951 to 1987 are shown in Fig. 2, standardised for age in each quinquennium on the simplified European population that has been adopted for this purpose by the International Agency for Research on Cancer (1976). For each disease, mortality rates in each period have been expressed as proportions of the rates in the early '50s.

Trends in mortality in men – England and Wales



The contrasts are striking; varying between progressive and substantial increase to progressive and substantial decrease. One disease, aortic aneurysm, which increased steadily throughout, increased over sixfold, which is so much more than any other that the scale of the graph for this disease has had to be different. For cancer of the lung, the mortality increased rapidly at first and then declined, while for cancer of the oesophagus it showed the reverse, a reduction followed by a rise. For cancers of the larynx and mouth and pharynx the mortality fell and then stabilised, while for chronic bronchitis and emphysema it continued to fall until the mid 1980s.

That the trends in mortality from the principal types of cancer caused by smoking have differed has been recognised for many years and has sometimes been used as an argument that smoking is not a principal cause of any of them. The evidence that it is a cause rests, however, not on the study of such trends, but on the much sounder footing of the comparison of affected and unaffected individuals. It is so strong that other explanations for the trends have to be sought and several are at hand.

The least interesting, but one which, I suspect, makes a contribution to the disproportionately great increase in mortality attributed to aortic aneurysm, is better diagnosis. Before 1950, aneurysm, other than in the ascending aorta due to syphilis, was seldom considered as a possible diagnosis in the absence of autopsy, and syphilitic aneurysms were classified under a separate head. It is likely therefore that in the 1950s a relatively high proportion of other aneurysms was overlooked or misclassified.

Secondly, there is the differential effect on different organs of the changes in the type of cigarette commonly smoked which, as Fig. 1 showed, delivered less than half as much tar in the 1980s as it did before 1940. There is good evidence, as I shall show later, that the reduction in the tar content of the smoke has had a substantial effect on the risk of lung cancer; but there is little or no evidence of an effect on the risk of diseases that are due to the absorption of chemicals from smoke into the blood and their distribution throughout the body. That this might be so is easy to understand, as low tar cigarettes are always low in nicotine and are smoked in a different way from cigarettes that deliver larger amounts, so as to obtain the same level of nicotine in the blood. The deep inhalation that occurs as a result may, therefore, spare the bronchi and reduce the risk of bronchial cancer, while exposing the vascular system and other distant organs (such as the bladder and pancreas) to unaltered amounts of the noxious chemicals.

Thirdly, there is the fact that the smoking of cigarettes, cigars, and pipes also has different effects on different organs. In many countries, and certainly in England and Wales, cigarette smoke is much more hazardous for the bronchi than the smoke of cigars and pipes, presumably because of variation in the physical distribution of the smoke; but all three methods of smoking have much the same effect on the risk of cancers of the mouth, pharynx, oesophagus, and epilarynx. As there has been much less change in the total amount of tobacco smoked than in the amount of cigarettes, it is only to be expected that the risk of lung cancer will have increased more than the risk of cancers of the sites that are equally related to the smoking of cigarettes, cigars, and pipes.

Fourthly, the mechanisms by which tobacco smoke causes disease differ and the temporal relations between the development of disease and the time of starting or stopping smoking must be expected to vary, depending on the precise mechanism involved. There is, however, no obvious reason why differences of this sort should cause differences in the trends of different types of cancer.

I fall back, therefore, on a fifth reason as the most likely explanation of the observed differences: namely, the fact that smoking acts synergistically with many other factors to cause disease, so that two or more factors in combination may serve to multiply each other's effect rather than add to them. Synergism in the production of cancer or myocardial infarction has been demonstrated between smoking and exposure to asbestos, the consumption of alcoholic drinks, diet, hypertension, and the use of steroid contraceptives, and there may be a similar relationship with atmospheric pollution by the combustion products of fossil fuels and perhaps also with ionising radiation, though, in the latter case, the effect of the synergism seems to be less than multiplicative. With so many such effects already recognised it would be surprising if there were not also many more.

So far as the diseases illustrated in Fig. 2 are concerned, three synergisms are likely to be of outstanding importance. One that is proved is the synergism with the consumption of alcohol. This multiplies the effect of smoking on the risk of cancers of the mouth, pharynx, larynx, and oesophagus, but not on the risk of cancer of the lung and it could have been responsible for the late change in the trend in the mortality from cancers of the upper aerodigestive tract, as the consumption of alcohol had been decreasing before 1950, but doubled between 1950 and 1980. A second synergism, which may also affect these cancers, is with diet. Nutritional factors, such as the consumption of fruit and yellow and green vegetables, are known to affect the incidence of these diseases (Esteve et al., 1990) and deficiencies of such factors almost certainly play a large part in causing the extremely high incidence of oesophageal cancer in parts of Africa and Asia. But whether this affects the incidence of cancers of the upper aerodigestive tract so much more than cancer of the bronchi has yet to be proved. Thirdly, there is a synergism with social conditions which may have contributed more to the reduction in mortality from chronic obstructive lung disease than has the reduction in atmospheric pollution during adult life. Barker and Osmond (1986), for example, have shown that infant mortality in British towns at the beginning of the century was closely and specifically correlated with the mortality from chronic obstructive lung disease fifty years later—much more so than it was with the mortality from lung cancer, the correlation coefficients for the two diseases being respectively 0.81 and 0.52 for males and 0.77 and 0.09 for females. We may, therefore, suggest as a hypothesis that the high rate of chest infection in childhood in the poorer sections of the population increased the individual's susceptibility to the effects of smoking in subsequent decades. The decrease that has occurred since the middle sixties would then be due to improved social conditions some decades earlier, and the dramatic fall at young ages, which has been much greater than in the standardised rate for all ages recorded in Fig. 2, could have been enhanced by

the introduction of sulphonamides and antibiotics for the treatment of childhood infections.

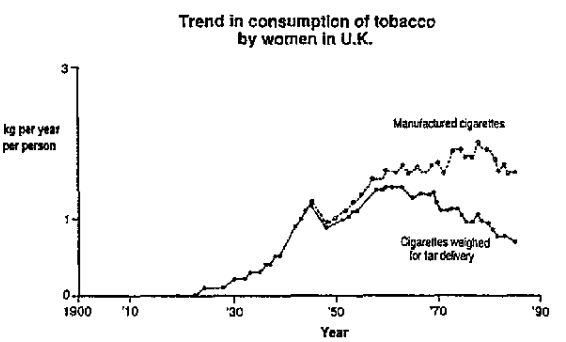
Trends in women

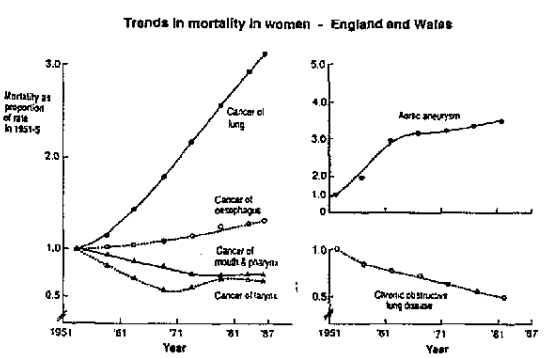
Time precludes a similar discussion of the trends in women, but Figs. 3 and 4 show that they are equally complex. Fig. 3 shows that tobacco smoking, almost wholly in the form of cigarettes, began only in the 1920s, rose sharply during the war and again in the 1950s, and began to decrease only in the late 1970s. It is understandable, therefore, that the mortality from cancer of the lung, which is largely determined by changes in smoking habits three or four decades earlier, should have continued to increase until now, as is shown in Fig. 4. The scale in the Figure, it will be noted, is different from that used to illustrate the trends for men, as the increase in mortality from cancer of the lung has been relatively so much greater (over 200 per cent compared to a maximum in this period of 75 per cent). The trends in the other five diseases, which are also illustrated in the Figure, are broadly similar to the trends in men, but differ in detail. In so far as they differ from those in men the differences can, I think, mostly be explained by differences in the consumption of tobacco and alcohol. The most notable difference is the lack of any increase in mortality from chronic obstructive lung disease until the last few years due, I suggest, to the relatively weak effect of cigarette smoking in the 1950s failing to compensate for the major improvements that were taking place in atmospheric pollution, and had taken place long before in social conditions in infancy.

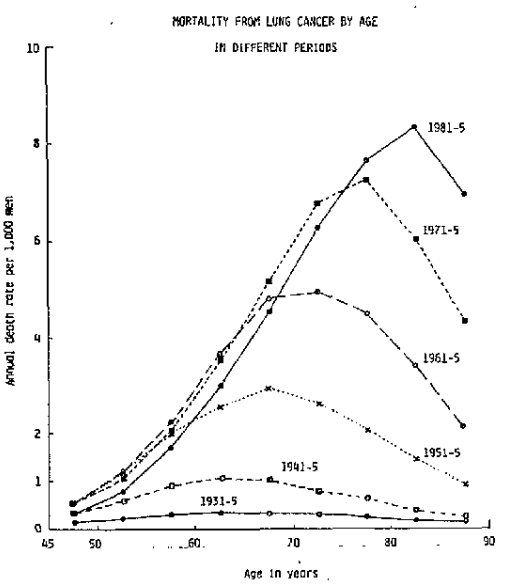
QUANTITATIVE PREDICTION OF TOBACCO RELATED DISEASE

I conclude from this analysis of past trends that the quantitative prediction of the future incidence of many of the diseases related to smoking is unlikely to be practicable without much more detailed knowledge than we now have of the factors other than tobacco that also contribute to their aetiology. For these diseases all we can say is that in the absence of smoking their incidence would be lower, and in some cases much lower, than in its presence.

For cancer of the lung, however, the position is different and the approximate trend can be predicted with confidence, due to the fact that smoking is of such overwhelming importance in its aetiology for the great majority of the people in most countries. The ability to predict the waxing of the epidemic was first drawn to our attention by Korteweg in 1951 when he demonstrated that the change in the age distribution of lung cancer corresponded with what would be expected if cohorts born at different times were exposed to increasing amounts of a carcinogenic agent. The evolution of the epidemic of lung cancer in England and Wales occurred almost precisely as Korteweg had predicted, as is shown for men in Fig. 5. The mortality at young ages reached its maximum in the late 1950s, but the rate at older ages continued to increase until it came in line with the rate to be expected from the standard pattern for epithelial tumours outside the reproductive system. By 1985 only the rate at 85 years and over was out of line. In the next two years, however, it increased by 4% while the rates at all younger ages fell. We can, therefore, be confident that Richard Peto's (1987) prediction that there will be 900,000 deaths a year from the disease in men in China by about the year 2025 will not be far out unless there are major changes in the people's smoking habits.







Prediction of the waning of the epidemic has been more difficult because of the uncertain effect of changes in the type of cigarette. We know that mortality ceases to increase, or rather increases only slowly at the rate that applies to non-smokers, immediately smoking is stopped; but the fall at young ages in men, who have mainly smoked only low tar cigarettes, illustrated in Fig. 5 but shown more clearly in Table 5, has been more than could be expected from the fall in mortality in consumption. This must be due mainly to the reduction in the tar content of the smoke, as the mortality has begun to fall in the last few years in young women as well as in young men, despite the progressive increase in consumption —a finding that has been duplicated in the United States, though later than in Britain, as consumption in the United States continued in increase for longer (Surgeon General, 1989).

Table 5

CHANGE IN MORTALITY FROM LUNG CANCER:

ENGLAND AND WALES, 1946 TO 1987

Age (yrs)	Period of maximum rate	% change 1986-87	Age (yrs)	Period of maximum rate	% change 1986-87
25-29	1946-50	-89	55-59	1956-60	-40
30-34	"	-78	60-64	1966-70	-25
35-39	1951-55	-61	65-69	"	-22
40-44	1956-60	-60	70-74	1971-75	-13
45-49	"	-54	75-79	1976-80	-10
50-54	"	-52	80-84	1981-85	-4
			85+	1986-87	-

Another factor that complicates prediction is the bias that now frequently affects the self-reporting of smoking habits. The existence of such a bias has been demonstrated in several countries, and most recently in Italy, where progressive and major falls in the reported proportion of smokers and in the average amount consumed have been accompanied by an increase in sales (Ferraroni et al., 1989). I have no doubt that sales figures are generally the more reliable and survey data need to be corrected for underestimation by sales figures, as they have been in the published report on trends in smoking habits in the UK (Wald et al.,1988).

But even if we cannot be sure about the precise effect of declining sales, because of the interfering effect of changes in the type of tobacco sold, we can be sure about the approximate size of the risk that will remain when smoking is eliminated altogether. There are of course other causes of lung cancer, but the most important of these (in the sense of the causes to which the mass of the population is exposed) seem to be relatively constant throughout the world and over time, for the rate in non-smokers has been recorded as being much the same in different areas and different ethnic groups and at different times, as is illustrated in Table 6. One exception is Chinese women, in whom an increased risk of lung cancer in non-smokers may be largely attributed to the singular habit of cooking with a wok (Gao al, 1987) and there may, of course, be others in populations that have not yet been intensively studied. For most of the world, however, we can be confident that, in the absence of smoking, the annual risk of developing the disease, standardised on the simplified world population used by the International Agency for Research on Cancer (1976)—which is, of course, a much younger population than that used for the rates in Table 6—would not be more than 4 or 5 per 100,000 in either sex, whereas the current rates are anything up to 20 times higher.

Table 6

MORTALITY FROM LUNG CANCER IN NON-SMOKERS

Population	Period of observation	Rate $10^{-5}y^{-1}$ Men	Women
USA			
American Cancer Society's volunteers			
Study (1)	1959-65	15.5	10.3
" (2)	1982-86	13.6	11.4
Veterans	1954-70	11.2	-
UK			
British doctors	1951-88	12.6	-
Sweden			
Random sample	1963-72	13.0	10.3
Japan			
Geographical sample	1966-82	17.8	-

CONCLUSION

Prediction of trends in disease is, I conclude, a much more difficult undertaking than might superficially be thought. The production of disease is a complex process to which many factors contribute and much further research will be required before they are all discovered and their individual roles fully understood. The smoking of tobacco causes many organs of the body to be exposed to many different toxic chemicals and is a factor in the production of many diseases and a principal factor in the production of some. We can be sure that increased smoking will increase the risk of all these diseases and that decreased smoking will decrease it, but it is only when smoking is overwhelmingly the principal factor that we can be at all precise about what the quantitative effects of changes in consumption are likely to be. We must not forget, however, that important as the latter diseases are, the greater total numbers of deaths that occur prematurely will be due to one or other of the many other diseases, the trends in which are more difficult to foretell.

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